REMARKS

Claims 1 through 15 are currently pending. Claim 13 has been amended to further clarify the claimed scope. Basis can be found throughout the application as filed, including the abstract and title

Rejection under 35 U.S.C. § 103

Claims 1 through 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoi et al. (hereinafter "*Aoi*") in view of the admission of the prior art, Gans et al. (hereinafter "Gans"), Banwart and Furia.

Specifically, the Office Action states that "*Aoi* et al. teach enteral complete solution . . . to prevent nutritional deficiency of cancer patients . . .however, are silent in teaching the particular type or amount of parabens, salts of benzoic acid and salts of sorbic acid."

In order to anticipate a composition when a reference discloses multiple variables and combinations, the reference must describe the composition with enough detail such that the composition is in the possession of the public. In re Brown, 329 F. 2d 1006, 1011, 141 U.S.P.Q. 245, 249 (C.C.P.A. 1964). The Examiner has asserted that Aoi discloses the use of salts of benzoic acid and salts of sorbic acids and esters of p-hydroxybenzoic acid, although Aoi is silent in teaching the particular type or amount of parabens, salts of benzoic acid and salts of sorbic acid." At column 4 lines 50-53 a number of preservatives and is "inclusive of their salts", however, under the obviousness standard, while it may be obvious to try to vary all parameters or try each of numerous possible choices, the reference must suggest the combination and selection of parameters for the composition. In re O'Farrell, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). The fact that parabens, salts of benzoic acid and salts of sorbic acids are recognized as preservatives does not give the public possession of the invention, and therefore the present invention would not flow naturally from the suggested prior art.

Although lists may include species (i.e. for illustration purposes: Products for cleaning floors comprising . . .) , the combination of 2 or more of the contained elements within the list in the right quantities can be very dangerous (i.e. ammonia and chlorine produces chloramine gasses that can damage the lungs; Chlorine bleach mixed with acid, which is used in some toilet bowl cleaners, forms toxic chlorine gas), other combinations may have inhibitory effects and incompatibilities (benzoic acid and kaolin; or sorbic acid and a number of compounds, methylparabens and some sugars and sugar alcohols). Please see the attached references from the "Handbook of Pharmaceutical Excipients". Just because two or more items are listed for the same use does not mean in combination they will be effective

and not dangerous. Therefore the combination of the parabens, benzoic and sorbic acids at the claimed ratios were found to have surprising and unexpected results, are not obvious.

Further, as noted by the Examiner, Aoi discloses the pH of their solution to be 5.5-7. As will be discussed later, the art disclosed limitation in the use some of the mentioned preservatives at various pH's.

The Applicants have surprisingly discovered that an alkyl paraben when used in combination with the salts of benzoic and sorbic acids in the amounts listed, resulted in an enhanced synergism when functioning as a preservative that is effective at pH's from 3-8, acid to base including neutral.

Now turning to the combination of Aoi with Gans, "Even if the teachings of a primary reference could be modified to arrive at the claimed subject matter, the modification is not obvious unless the prior art also suggests the desirability of such a modification." In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed Cir. 1989). Further, "Where the prior art gives no indication of which parameters are critical and no direction as to which of many possible choices is likely to be successful, the fact that the claimed combination falls within the scope of possible combinations taught therein does not render it unpatentably obvious. In re O'Farrell, 7 U.S.P.Q 1673 (CAFC 1988)

The nutritional compositions disclosed in Gans are not complete feeding solutions. As previously admitted by the Examiner, Gans teaches or suggests solutions that expressly exclude fat, which is a macronutrient required for a complete feeding solution. In column 2, lines 47 through 58, Gans distinguishes its disclosed nutritional compositions from those of the prior art by the very fact that they lack triglycerides. Although Gans does teach some amounts and of parabens and salts or sorbic or benzoic, there is no teaching to suggest that the same parameters would work with the addition of the fats. As previously presented, the addition of fats could modify the composition of Gans in a way that would cause failure of the preservative system or the formation of undesirable by-products. There is no teaching or suggestion in Gans that his formulation would be successful with the addition of fats. The Examiner has stated in the present Office Action that "one of ordinary skill in the art would presume that the preservative compositions of Gans et al. would be compatible with the fat-containing solution of Aoi". The ultimate legal conclusion of obviousness must be based on facts or records, not on the Examiner's unsupported allegation that a particular structural modification is "well known" and thus obvious. Subjective opinions are of little weight against contrary evidence. In re Wagner et al. 152 USPQ 552 (CCPA 1967). Because of the hydrophobicity of the parabens, the skilled person would have expected that when added to a tube feeding composition containing fat, these agents would have accumulated in the lipid phase to the exclusion of the aqueous phase. The predictable consequence thereof would

have been an ineffectiveness to combat growth of harmful microorganisms in the aqueous phase of the composition, and therefore insufficient prevention of tube clogging.

Further, at column 3, lines 25-26, Gans states that the solution must have a necessary acid pH, which would limit its utility, unlike the present invention which is effective in a pH range of 3-8.

The Examiner has stated that Gans discloses .4-1% preservatives, it is noted that .4-1 is not percent, but parts by weight, this would render the example at column 4, lines 20-33 to be .2 to 3.6% preservatives, and does not mention which preservatives are used or in what ratios. Where the prior art gives no indication of which parameters are critical and no direction as to which of many possible choices is likely to be successful, the fact that the claimed combination falls within the scope of possible combinations taught therein does not render it unpatentably obvious. In re O'Farrell, 7 U.S.P.Q 1673 (CAFC 1988)

The Examiner states that Gans teaches .12% of potassium sorbate and sodium benzoate as well as 0.05% propyl paraben and 0.12% methyl paraben as recited in Claims 1 and 8. Applicant respectfully disagrees with this assertion. Claim 1 and 8 claim a range of 0.1-0.2% by weight of the pharmaceutically acceptable salts of benzoic and sorbic acids. The combination of the sorbate and benzoate would be 0.24%, outside the disclosed range necessary for the present invention.

The Examiner states that Branwart is relied on as evidence of the conventional properties of preservatives taught by Aoi. The Examiner states that potassium sorbate and sodium Benzoate have better solubility over sorbic and bezoic acid, however, there is no mention of this effect exists when the sorbic and benzoic acids are combined as in the present formulation. Branwart states that Benzoic acid needs a low pH to be effective (middle 393). Branwart further shows limits of potasium sorbate not being effective and detrimental in maintaining foods during refrigerated storage. Further, Branwart states that "[c]ombinations of benzoate and sorbate are <u>believed to be more effective</u> [emphasis added] that either chemical used alone", however, Branwart offers no proof or level of improvement, contrary to the Examiner's assertion that "sorbates in combination with benzoates are <u>far more</u> [emphasis added] effective than either used alone."

Examiner states that Furia is relied on to show the conventional use of parabens in food formulations, using parabens as more effective preservatives against molds at neutral/high pH that sorbis and benzoic acid and use of sodium benzoates and parabens cumulative antimicrobial effect. Applicant notes that on page 124 shows at pH of 7 and above benzoic acid and sorbic acid did not inhibit mold at tested concentrations and on page 125 parabens are most active against molds and yeast and less effective against bacteria, especially gram negative. In regards to the use of sodium benzoates and parabens cumulative antimicrobial effect, based on Branwart's teaching of Benzoic acid needs a low

pH to be effective, and Parabens being effect at higher pH (including neutral), according to the prior art presented by the Examiner that this cumulative effect must occur at a narrow pH range. The Applicants have surprisingly discovered that an alkyl paraben when used in combination with the salts of benzoic and sorbic acids in the amounts listed, resulted in an enhanced synergism when functioning as a preservative that is effective at pH's from 3-8, acid to base including neutral.

Thus, because there is no motivation to combine *Aoi*, Branwart, *Gans* and *Furia*, and because there's no reasonable expectation of success, then the Examiner has not set forth a *prima facie* case of obviousness thus rendering this rejection improper. The Applicants respectfully request that this rejection be withdrawn.

Regarding claim 10, since claim 1 is believed to be patentable, and claim 10 further limits and depends from claim 1, claim 10 is believed patentable.

Claims 13 through 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Gans* in view of *Aoi*. Similar to the prior discussion for Claims 1 through 12, Applicants respectfully submit that a *prima facie* case of obviousness has also not been established. Although Gans does teach some amounts and of parabens and salts or sorbic or benzoic, there is no teaching to suggest that the same parameters would work with the addition of the fats.

Examiner states Gans "presumably would inhibit the growth of fungus, gram negative or gram-positive bacteria as recited since that is the purpose of "preserving,"" however, the Examiner offers no support for this assertion. As stated above, at the varying pH's, the different preservatives have different efficacies and targets of actions. See In re Wagner et al. 152 USPQ 552 (CCPA 1967) (quoted above)

The reference must clearly and unequivocally disclose the composition or direct those skilled in the art to the composition without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the reference. In re Arkley, 455 F.2d 586, 587, 172 U.S.P.Q. 524, 526 (C.C.P.A. 1972). Additionally, under the obviousness standard, while it may be obvious to try to vary all parameters or try each of numerous possible choices, the reference must suggest the combination and selection of parameters for the composition. In re O'Farrell, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990). Therefore, based on the arguments above it would not have been obvious to modify Aoi with Branwart, Furia and Gans to achieve the present invention.

Thus, in view of the foregoing arguments, Applicants respectfully request reconsideration of the present application. If a telephone interview would be of assistance in

advancing the prosecution of this application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

Respectfully submitted,

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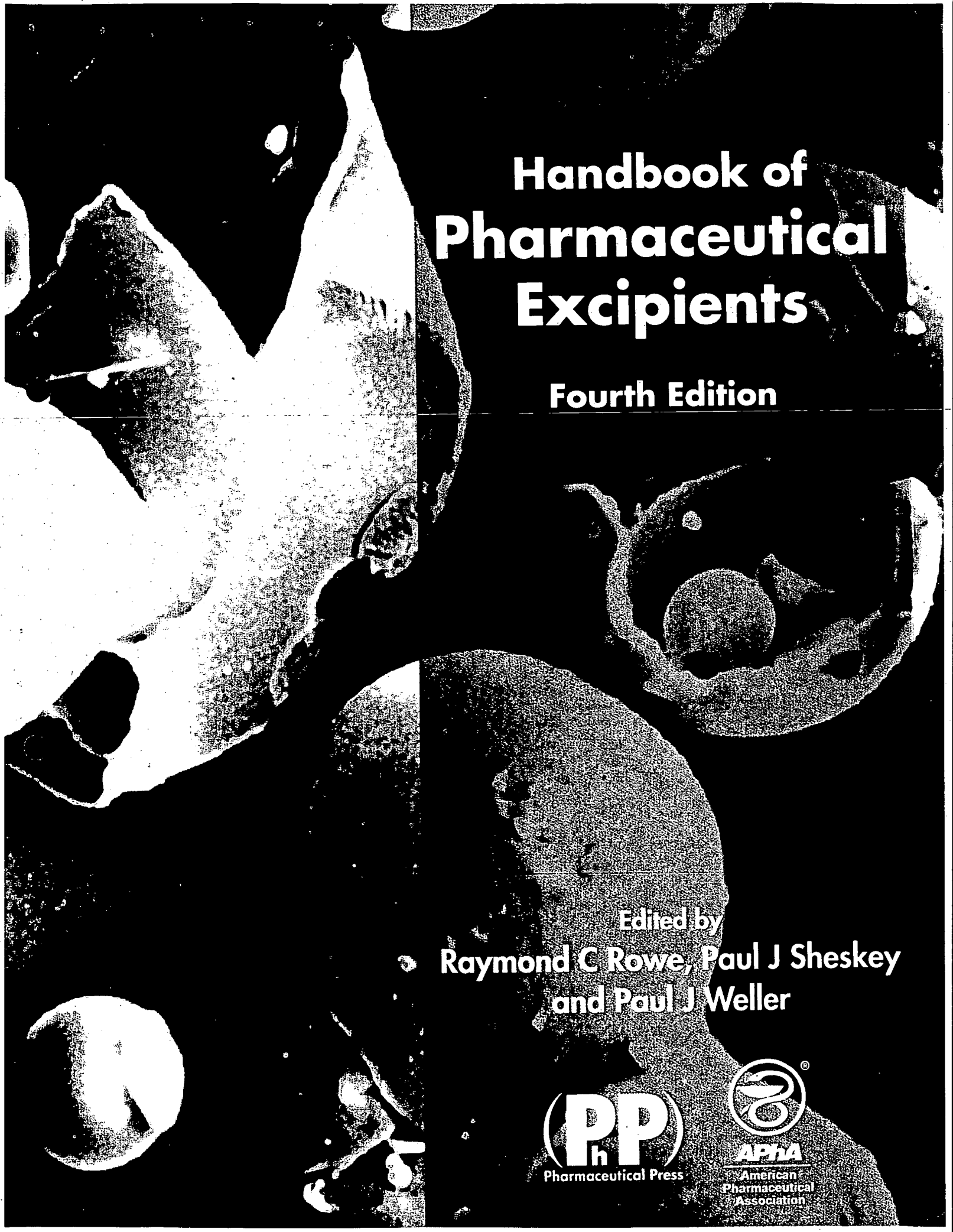


Handbook of Pharmaceutical Excipients

Fourth Edition

Edited by
Raymond C Rowe, Paul J Sheskey
and Paul J Weller

Pharmaceutical Press
APhA American Pharmaceutical Association

Benzoic Acid

1 Nonproprietary Names

BP: Benzoic acid
JP: Benzoic acid
PhEur: Acidum benzoicum
USP: Benzoic acid

2 Synonyms

Benzenecarboxylic acid; benzeneformic acid; carboxybenzene; dracylic acid; E210; phenylcarboxylic acid; phenylformic acid.

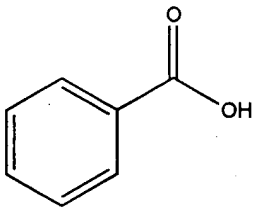
3 Chemical Name and CAS Registry Number

Benzoic acid [65-85-0]

4 Empirical Formula and Molecular Weight

$C_7H_6O_2$ 122.12

5 Structural Formula



6 Functional Category

Antimicrobial preservative; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Benzoic acid is widely used in cosmetics, foods, and pharmaceuticals (*see* Table I), as an antimicrobial preservative.[1–3] Greatest activity is seen at pH values between 2.5–4.5; *see* Section 10.

Benzoic acid also has a long history of use as an antifungal agent[4] in topical therapeutic preparations such as Whitfield's ointment (benzoic acid 6% and salicylic acid 3%).

Table I: Uses of benzoic acid.

Use	Concentration (%)
IM and IV injections	0.17
Oral solutions	0.01–0.1
Oral suspensions	0.1
Oral syrups	0.15
Topical preparations	0.1–0.2
Vaginal preparations	0.1–0.2

8 Description

Benzoic acid occurs as feathery, light, white or colorless crystals or powder. It is essentially tasteless and odorless or with a slight characteristic odor suggestive of benzoin.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for benzoic acid.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Characters	—	+	—
Congealing range	121–124°C	121–124°C	121–123°C
Water	≤0.5%	—	≤0.7%
Residue on ignition	≤0.05%	—	≤0.05%
Sulfated ash	—	≤0.1%	—
Readily carbonizable substances	+	+	+
Readily oxidizable substances	+	+	+
Heavy metals	≤20 ppm	≤10 ppm	≤0.001%
Halogenated compounds and halides	+	≤300 ppm	—
Appearance of solution	—	+	—
Assay	≥99.5%	99.0–100.5%	99.5–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 2.8 (saturated aqueous solution at 25°C)

Antimicrobial activity: only the undissociated acid shows antimicrobial properties, the activity therefore depends on the pH of the medium. Optimum activity occurs at pH values below 4.5; at values above pH 5, benzoic acid is almost inactive.[5] It has been reported that antimicrobial activity is enhanced by the addition of protamine, a basic protein.[6]

Bacteria: moderate bacteriostatic activity against most species of Gram-positive bacteria. Typical MIC is 100 µg/mL. Activity is less, in general, against Gram-negative bacteria. MIC for Gram-negative bacteria may be up to 1600 µg/mL.

Molds: moderate activity. Typical MICs are 400–1000 µg/mL at pH 3; 1000–2000 µg/mL at pH 5.

Spores: inactive against spores.

Yeasts: moderate activity. Typical MIC is 1200 µg/mL. The addition of propylene glycol may enhance the fungistatic activity of benzoic acid.

Autoignition temperature: 570°C

Boiling point: 249.2°C

Density:
1.311 g/cm^3 for solid at 24°C
1.075 g/cm^3 for liquid at 130°C

Dissociation constant: the dissociation of benzoic acid in mixed solvents is dictated by specific solute–solvent interactions as well as by relative solvent basicity. Increasing the organic solvent fraction favors the free acid form.[7]
pK_a = 4.19 at 25°C
pK_a = 5.54 in methanol 60%
Flash point: 121–131°C
Melting point: 122°C (begins to sublime at 100°C).
Moisture content: 0.17–0.42% w/w
Partition coefficients:
Benzene : water = 0.0044[8]
Cyclohexane : water = 0.30[9]
Octanol : water = 1.87[10]
Refractive index:
n_D^{15} = 1.5397 for solid
n_D^{132} = 1.504 for liquid
Solubility: apparent aqueous solubility of benzoic acid may be enhanced by the addition of citric acid or sodium acetate to the solution; *see* Table III.

Table III: Solubility of benzoic acid.

Solvent	Solubility at 25°C unless otherwise stated
Acetone	1 in 2.3
Benzene	1 in 9.4
Carbon disulfide	1 in 30
Carbon tetrachloride	1 in 15.2
Chloroform	1 in 4.5
Cyclohexane	1 in 14.6[9]
Ethanol	1 in 2.7 at 15°C
	1 in 2.2
Ethanol (76%)	1 in 3.72[11]
Ethanol (54%)	1 in 6.27[11]
Ethanol (25%)	1 in 68[11]
Ether	1 in 3
Fixed oils	Freely soluble
Methanol	1 in 1.8
Toluene	1 in 11
Water	1 in 300

11 Stability and Storage Conditions

Aqueous solutions of benzoic acid may be sterilized by autoclaving or by filtration.

A 0.1% w/v aqueous solution of benzoic acid has been reported to be stable for at least 8 weeks when stored in polyvinyl chloride bottles, at room temperature.[12]

When added to a suspension, benzoic acid dissociates, with the benzoate anion adsorbing onto the suspended drug particles. This adsorption alters the charge at the surface of the particles, which may in turn affect the physical stability of the suspension.[13]

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Undergoes typical reactions of an organic acid, e.g. with alkalis or heavy metals. Preservative activity may be reduced by interaction with kaolin.[14]

13 Method of Manufacture

Although benzoic acid occurs naturally, it is produced commercially by several synthetic methods. One process involves the continuous liquid-phase oxidation of toluene in the presence of a cobalt catalyst at 150–200°C and 0.5–5.0 MPa (5.0–50.0 atm) pressure to give a yield of approximately 90% benzoic acid.

Benzoic acid can also be produced commercially from benzotrichloride or phthalic anhydride. Benzotrichloride, produced by chlorination of toluene, is reacted with 1 mole of benzoic acid to yield 2 moles of benzoyl chloride. The benzoyl chloride is then converted to 2 moles of benzoic acid by hydrolysis. Yield is 75–80%.

In another commercial process, phthalic anhydride is converted to benzoic acid, in about an 85% yield, by hydrolysis in the presence of heat and chromium and disodium phthalates.

Crude benzoic acid is purified by sublimation or recrystallization.

14 Safety

Ingested benzoic acid is conjugated with glycine in the liver to yield hippuric acid, which is then excreted in the urine;[15] care should be taken when administering benzoic acid to patients with chronic liver disease.[16] Benzoic acid is a gastric irritant, and a mild irritant to the skin.[17–19] It is also a mild irritant to the eyes and mucous membranes.[20] Allergic reactions to benzoic acid have been reported, although a controlled study indicated that the incidence of urticaria in patients given benzoic acid is no greater than in those given a lactose placebo.[21]

The WHO acceptable daily intake of benzoic acid and other benzoates, calculated as benzoic acid, has been set at up to 5 mg/kg body-weight.[22,23] The minimum lethal human oral dose of benzoic acid is 500 mg/kg body-weight.[24]

LD_{50} (cat, oral): 2 g/kg[24]
LD_{50} (dog, oral): 2 g/kg
LD_{50} (mouse, IP): 1.46 g/kg
LD_{50} (mouse, oral): 1.94 g/kg
LD_{50} (rat, oral): 1.7 g/kg
See also Sodium benzoate.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzoic acid may be harmful by inhalation, ingestion, or skin absorption and may be irritant to the eyes, skin, and mucous membranes. Benzoic acid should be handled in a well-ventilated environment; eye protection, gloves, and a dust mask or respirator are recommended. Benzoic acid is flammable.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM and IV injections, irrigation solutions, oral solutions, suspensions, syrups and tablets, rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Sodium benzoate.

Sorbic Acid

1 Nonproprietary Names

BP: Sorbic acid
PhEur: Acidum sorbicum
USPNF: Sorbic acid

2 Synonyms

E200; (2-butenylidene) acetic acid; crotylidene acetic acid; hexadienic acid; hexadienoic acid; 2,4-hexadienoic acid; 1,3-pentadiene-1-carboxylic acid; 2-propenylacrylic acid; (*E*,*E*)-sorbic acid; *Sorbistat K*.

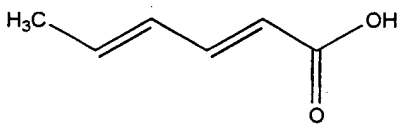
3 Chemical Name and CAS Registry Number

(*E*,*E*)-Hexa-2,4-dienoic acid [22500-92-1]

4 Empirical Formula and Molecular Weight

$C_6H_8O_2$ 112.13

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Sorbic acid is an antimicrobial preservative[1] with antibacterial and antifungal properties used in pharmaceuticals, foods, enteral preparations, and cosmetics. Generally, it is used at concentrations of 0.05–0.2% in oral and topical pharmaceutical formulations, especially those containing nonionic surfactants. Sorbic acid is also used with proteins, enzymes, gelatin, and vegetable gums.[2] It has been shown to be an effective preservative for promethazine hydrochloride solutions in a concentration of 1 g/L.[3]

Sorbic acid has limited stability and activity against bacteria and is thus frequently used in combination with other antimicrobial preservatives or glycols, when synergistic effects appear to occur; *see* Section 10.

8 Description

Sorbic acid is a tasteless, white to yellow-white crystalline powder with a faint characteristic odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sorbic acid.

Test	PhEur 2002	USPNF 20
Identification	+	+
Appearance of solution	+	—
Melting range	132–136°C	132–135°C
Water	≤1.0%	≤0.5%
Residue on ignition	—	≤0.2%
Sulfated ash	≤0.2%	—
Heavy metals	≤10 ppm	≤0.001%
Aldehyde (as C_2H_4O)	≤0.15%	—
Organic volatile impurities	—	+
Assay (anhydrous basis)	99.0–101.0%	99.0–101.0%

10 Typical Properties

Antimicrobial activity: sorbic acid is primarily used as an antifungal agent, although it also possesses antibacterial properties. The optimum antibacterial activity is obtained at pH 4.5; and practically no activity is observed above pH 6.[4,5] The efficacy of sorbic acid is enhanced when it is used in combination with other antimicrobial preservatives or glycols since synergistic effects occur.[6] Reported minimum inhibitory concentrations (MICs) at pH 6 are shown in Table II.[7]

Table II: Minimum inhibitory concentrations (MICs) of sorbic acid at pH 6.

Microorganism	MIC (μg/mL)
Aspergillus niger	200–500
Candida albicans	25–50
Clostridium sporogenes	100–500
Escherichia coli	50–100
Klebsiella pneumoniae	50–100
Penicillium notatum	200–300
Pseudomonas aeruginosa	100–300
Pseudomonas cepacia	50–100
Pseudomonas fluorescens	100–300
Saccharomyces cerevisiae	200–500
Staphylococcus aureus	50–100

Boiling point: 228°C with decomposition.
Density: 1.20 g/cm^3
Dissociation constant: pK_a = 4.76
Flash point: 127°C
Melting point: 134.5°C

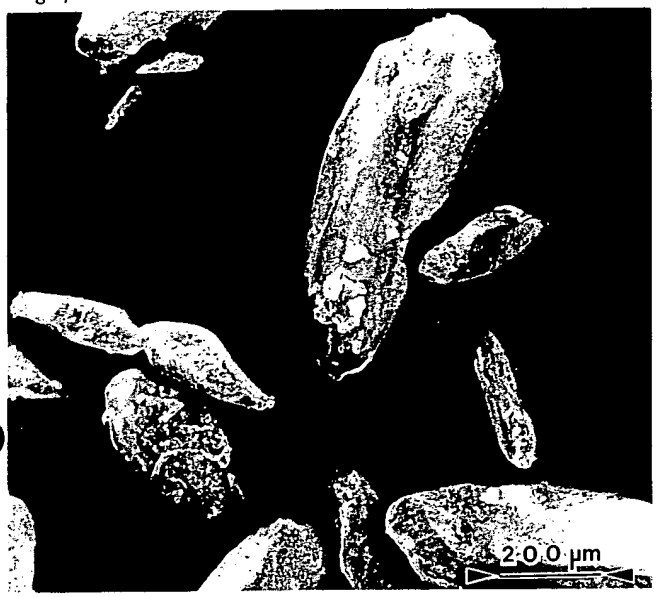
Solubility: *see* Table III. In syrup, the solubility of sorbitol decreases with increasing sugar content.

Table III: Solubility of sorbic acid.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	1 in 11
Chloroform	1 in 15
Ethanol	1 in 8
Ethanol (95%)	1 in 10
Ether	1 in 30
Glycerin	1 in 320
Methanol	1 in 8
Propylene glycol	1 in 19
Water	1 in 400 at 30°C 1 in 26 at 100°C

Vapor pressure: <1.3 Pa (<0.01 mmHg) at 20°C

SEM: 1
Excipient: Sorbic acid
Manufacturer: Pfizer Ltd.
Magnification: 60×



11 Stability and Storage Conditions

Sorbic acid is sensitive to oxidation, particularly in the presence of light; oxidation occurs more readily in aqueous solution than in the solid form. Sorbic acid may be stabilized by phenolic antioxidants such as 0.02% propyl gallate.[6]

Sorbic acid is combustible when exposed to heat or flame. When heated to decomposition, it emits acrid smoke and irritating fumes. The bulk material should be stored in a well-closed container, protected from light, at a temperature not exceeding 40°C.

12 Incompatibilities

Sorbic acid is incompatible with bases, oxidizing agents, and reducing agents. Some loss of antimicrobial activity occurs in the presence of nonionic surfactants and plastics. Oxidation is catalyzed by heavy-metal salts. Sorbic acid will also react with sulfur-containing amino acids, although this can be prevented by the addition of ascorbic acid, propyl gallate, or butylhydroxytoluene.

When stored in glass containers, the solution becomes very pH sensitive; therefore, preparations using sorbic acid as a preservative should be tested for their microbial purity after prolonged periods of storage.

Aqueous solutions of sorbic acid without the addition of antioxidants are rapidly decomposed when stored in polypropylene, polyvinylchloride, and polyethylene containers.

13 Method of Manufacture

Naturally occurring sorbic acid may be extracted as the lactone (parasorbic acid) from the berries of the mountain ash *Sorbus aucuparia* L. (Fam. Rosaceae). Synthetically, sorbic acid may be prepared by the condensation of crotonaldehyde and ketene in the presence of boron trifluoride; by the condensation of crotonaldehyde and malonic acid in pyridine solution; or from 1,1,3,5-tetraalkoxyhexane. Fermentation of sorbaldehyde or sorbitol with bacteria in a culture medium has also been used.

14 Safety

Sorbic acid is used as an antimicrobial preservative in oral and topical pharmaceutical formulations and is generally regarded as a nontoxic material. However, adverse reactions to sorbic acid and potassium sorbate, including irritant skin reactions[8–11] and allergic hypersensitivity skin reactions (which are less frequent), have been reported.[12–14]

Other adverse reactions that have been reported include exfoliative dermatitis due to ointments that contain sorbic acid,[15] and allergic conjunctivitis caused by contact lens solutions preserved with sorbic acid.[16]

No adverse reactions have been described after systemic administration of sorbic acid, and it has been reported that it can be ingested safely by patients who are allergic to sorbic acid.[17] However, peroral contact urticaria has been reported.[11]

The WHO has set an estimated total acceptable daily intake for sorbic acid, calcium sorbate, potassium sorbate, and sodium sorbate, expressed as sorbic acid, at up to 25 mg/kg body-weight.[18,19]

Animal toxicological studies have shown no mammalian carcinogenicity or teratogenicity for sorbic acid consumed at up to 10% of the diet.[20]

LD_{50} (mouse, IP): 2.82 g/kg[21]
LD_{50} (mouse, oral): 3.20 g/kg
LD_{50} (mouse, SC): 2.82 g/kg
LD_{50} (rat, oral): 7.36 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sorbic acid can be irritant to the skin, eyes, and respiratory system. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules, solutions, syrups, tablets, and topical preparations). Included in nonparenteral medicines licensed in the UK.

Table VI: Predicted rate constants and half-lives for methylparaben dissolved in dilute hydrochloric acid solution, at 25°C.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (hour^{-1})	Half-life $t_H \pm \sigma^{(a)}$ (day)
1	$(1.086 \pm 0.005) \times 10^{-4}$	266 ± 13
2	$(1.16 \pm 0.12) \times 10^{-5}$	2490 ± 260
3	$(6.1 \pm 1.5) \times 10^{-7}$	47000 ± 12000
4	$(3.27 \pm 0.64) \times 10^{-7}$	88000 ± 17000

[a] Indicates the standard error.

Table VII: Predicted remaining amount of methylparaben dissolved in dilute hydrocholoric acid solution, after autoclaving.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (hour^{-1})	Predicted residual amount after autoclaving (%)
1	$(4.96 \pm 0.16) \times 10^{-1}$	84.77 ± 0.46
2	$(4.49 \pm 0.37) \times 10^{-2}$	98.51 ± 0.12
3	$(2.79 \pm 0.57) \times 10^{-3}$	99.91 ± 0.02
4	$(1.49 \pm 0.22) \times 10^{-3}$	99.95 ± 0.01

[a] Indicates the standard error.

12 Incompatibilities

The antimicrobial activity of methylparaben and other parabens is considerably reduced in the presence of nonionic surfactants, such as polysorbate 80, as a result of micellization.[10,11] However, propylene glycol (10%) has been shown to potentiate the antimicrobial activity of the parabens in the presence of nonionic surfactants and prevents the interaction between methylparaben and polysorbate 80.[12]

Incompatibilities with other substances, such as bentonite,[13] magnesium trisilicate,[14] talc, tragacanth,[15] sodium alginate,[16] essential oils,[17] sorbitol,[18] and atropine,[19] have been reported. It also reacts with various sugars and related sugar alcohols.[20]

Absorption of methylparaben by plastics has also been reported; the amount absorbed is dependent upon the type of plastic and the vehicle. It has been claimed that low-density and high-density polyethylene bottles do not absorb methylparaben.[21]

Methylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

13 Method of Manufacture

Methylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with methanol.

14 Safety

Methylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics and oral and topical pharmaceutical formulations. Although parabens have also been used as preservatives in injections and ophthalmic preparations, they are now generally regarded as being unsuitable for these types of formulations owing to the irritant potential of the parabens. These experiences may depend on immune responses to enzymatically formed metabolites of the parabens in the skin.

Parabens are nonmutagenic, nonteratogenic, and noncarcinogenic. Sensitization to the parabens is rare, and these compounds do not exhibit significant levels of photocontact sensitization or phototoxicity.

Hypersensitivity reactions to parabens, generally of the delayed type and appearing as contact dermatitis, have been reported. However, given the widespread use of parabens as preservatives, such reactions are relatively uncommon; the classification of parabens in some sources as high-rate sensitizers may be overstated.[22]

Immediate hypersensitivity reactions following injection of preparations containing parabens have also been reported.[23–25] Delayed-contact dermatitis occurs more frequently when parabens are used topically, but has also been reported to occur after oral administration.[26–28]

Unexpectedly, preparations containing parabens may be used by patients who have reacted previously with contact dermatitis provided they are applied to another, unaffected, site. This has been termed the paraben paradox.[29]

Concern has been expressed over the use of methylparaben in infant parenteral products because bilirubin binding may be affected, which is potentially hazardous in hyperbilirubinemic neonates.[30]

The WHO has set an estimated total acceptable daily intake for methyl-, ethyl-, and propylparabens at up to 10 mg/kg body-weight.[31]

LD_{50} (dog, oral): 3.0 g/kg[32]
LD_{50} (mouse, IP): 0.96 g/kg
LD_{50} (mouse, SC): 1.20 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Methylparaben may be irritant to the skin, eyes, and mucous membranes and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

Methylparaben and propylparaben are affirmed GRAS Direct Food Substances in the USA at levels up to 0.1%. All esters except the benzyl ester are allowed for injection in Japan. In cosmetics, the EU and Brazil allow use of each paraben at 0.4%, but the total of all parabens may not exceed 0.8%. The upper limit in Japan is 1.0%.

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections; ophthalmic preparations; oral capsules, tablets, solutions and suspensions; otic, rectal, topical, and vaginal preparations). Included in medicines licensed in the UK.

17 Related Substances

Butylparaben; ethylparaben; methylparaben potassium; methylparaben sodium; propylparaben.

Methylparaben potassium
Empirical formula: $C_8H_7KO_3$
Molecular weight: 190.25
CAS number: [26112-07-2]
Synonyms: methyl 4-hydroxybenzoate potassium salt; potassium methyl hydroxybenzoate.

10 Typical Properties

Acid value: *see* Table VII.
Acidity/alkalinity: pH = 6.0–8.0 for a 5% w/v aqueous solution.
Flash point: 149°C
HLB value: *see* Table VIII.
Hydroxyl value: *see* Table VII.
Moisture content: *see* Table VII.
Saponification value: *see* Table VII.
Solubility: *see* Table IX .
Specific gravity: *see* Table VIII.
Surface tension: for 0.1% w/v solutions, *see* Table X.
Viscosity (dynamic): *see* Table VIII.

Table VII: Typical properties of selected polysorbates.

Polysorbate	Acid value (%)	Hydroxyl value	Moisture content	Saponification value
Polysorbate 20	2.0	96–108	3.0	40–50
Polysorbate 21	3.0	225–255	3.0	100–115
Polysorbate 40	2.0	90–105	3.0	41–52
Polysorbate 60	2.0	81–96	3.0	45–55
Polysorbate 61	2.0	170–200	3.0	95–115
Polysorbate 65	2.0	44–60	3.0	88–98
Polysorbate 80	2.0	65–80	3.0	45–55
Polysorbate 81	2.0	134–150	3.0	96–104
Polysorbate 85	2.0	39–52	3.0	80–95
Polysorbate 120	2.0	65–85	5.0	40–50

Table VIII: Typical properties of selected polysorbates.

Polysorbate	HLB value	Specific gravity at 25°C	Viscosity (mPa s)
Polysorbate 20	16.7	1.1	400
Polysorbate 21	13.3	1.1	500
Polysorbate 40	15.6	1.08	500
Polysorbate 60	14.9	1.1	600
Polysorbate 61	9.6	1.06	Solid
Polysorbate 65	10.5	1.05	Solid
Polysorbate 80	15.0	1.08	425
Polysorbate 81	10.0	—	450
Polysorbate 85	11.0	1.00	300
Polysorbate 120	14.9	—	—

Table IX: Solubilities of selected polysorbates in various solvents.

Polysorbate	Solvent			
	Ethanol	Mineral oil	Vegetable oil	Water
Polysorbate 20	S	I	I	S
Polysorbate 21	S	I	I	D
Polysorbate 40	S	I	I	S
Polysorbate 60	S	I	I	S
Polysorbate 61	SW	SW	SWT	D
Polysorbate 65	SW	SW	DW	D
Polysorbate 80	S	I	I	S
Polysorbate 81	S	S	ST	D
Polysorbate 85	S	I	ST	D
Polysorbate 120	S	I	I	S

D = dispersible; I = insoluble S = soluble; T = turbid; W = on warming.

Table X: Surface tension of related polysorbates.

Polysorbate	Surface tension at 20°C (mN/m)
Polysorbate 21	34.7
Polysorbate 40	41.5
Polysorbate 60	42.5
Polysorbate 61	41.5
Polysorbate 80	42.5
Polysorbate 85	41.0

11 Stability and Storage Conditions

Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. The oleic acid esters are sensitive to oxidation. Polysorbates are hygroscopic and should be examined for water content prior to use and dried if necessary. Also, in common with other polyoxyethylene surfactants, prolonged storage can lead to the formation of peroxides.

Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Discoloration and/or precipitation occur with various substances, especially phenols, tannins, tars, and tarlike materials. The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.[2] *See* Methylparaben.

13 Method of Manufacture

Polysorbates are prepared from sorbitol in a three-step process. Water is initially removed from the sorbitol to form a sorbitan (a cyclic sorbitol anhydride). The sorbitan is then partially esterified with a fatty acid, such as oleic or stearic acid, to yield a hexitan ester. Finally, ethylene oxide is chemically added in the presence of a catalyst to yield the polysorbate.

14 Safety

Polysorbates are widely used in cosmetics, food products, and oral, parenteral, and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. There have, however, been occasional reports of hypersensitivity to polysorbates following their topical and intramuscular use.[3] Polysorbates have also been associated with serious adverse effects, including some deaths, in low-birthweight infants intravenously administered a vitamin E preparation containing a mixture of polysorbates 20 and 80.[4,5] When heated to decomposition, the polysorbates emit acrid smoke and irritating fumes.

The WHO has set an estimated acceptable daily intake for polysorbates 20, 40, 60, 65, and 80, calculated as total polysorbate esters, at up to 25 mg/kg body-weight.[6]

Polysorbate 20: moderate toxicity by IP and IV routes. Moderately toxic by ingestion. Human skin irritant.
LD_{50} (hamster, oral): 18 g/kg[7]
LD_{50} (mouse, IV): 1.42 g/kg
LD_{50} (rat, oral): 37 g/kg
Polysorbate 21: moderately toxic by IV route.
Polysorbate 40: LD_{50} (rat, IV): 1.58 g/kg.[7] Moderately toxic by IV route.